A new insight into human Caspase- 12 using Homology modeling, Molecular Dynamics Simulation and Docking studies

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Introduction and Background: Alzheimer's disease is a chronic progressive neurodegenerative disorder which is caused by deposition of amyloid ß peptide (Aß) in brain tissue, thus formation of neurofibrillary tangles containing tau protein, results in an imbalance between Aß production and Aß clearance. The amyloid-ß (Aß) protein has been shown to induce neuronal cell death. Caspase- 12, which is located on cytoplasmic side of the ER in neuronal cells, is regarded as the major representative molecular marker of ER stress related cell death. Overexpression of caspase- 12 induces apoptosis, thus, caspase- 12 mediates an ER specific apoptosis pathway and may contribute to amyloid-ß neurotoxicity. Results indicate that caspase- 12 is specifically required for apoptosis induced by Aß protein and other ER stress-inducing signals, but is not normally involved in other apoptotic pathways. These results suggest that the human orthologue of caspase- 12 may be a potential therapeutic target for Alzheimer's disease.
Methods: In this study, homology modeling studies were performed to obtain a reasonable structure of the protein using known templates. A homology model for caspase- 12 protein was generated using modeler 9v12 software and its molecular dynamics (MD) simulation was performed using Gromacs software. The final model was validated using ERRAT score and Ramachandran plot at PROCHECK web server.
Result: 3D structure of caspase- 12 has been established by homology modeling. In order to cluster the obtained trajectories of simulation the root mean square deviation of Cα atoms were used.
Discussion and Conclusion: The presented model of caspase- 12 could be a starting point in future studies of drug design in Alzheimer's disease.

Keywords: Caspase- 12, Homology Modeling, Alzheimer's disease, Amyloid-ß, Molecular Dynamics Simulation

Amino Acid Decomposition Analysis of Natural Anthraquinones within Cancer Relevant Chemotherapeutic Targets

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Introduction and Background: A set of natural anthraquinones (AQs) were subjected to the combined in silico structure-based/quantum mechanical studies versus cancer relevant biochemical targets with the aim of proposing favorable anticancer mechanism(s). Selected chemotherapeutic targets were formerly known to be inhibited by AQs.
Methods: Genetic algorithm of AutoDock version 4.2 with incorporated MGL tools- 1.5.7 was applied to elucidate the most probable binding interactions of selected natural AQs within active sites of cancer-relevant targets. Subsequently, docked AQ molecules were subjected to amino acid decomposition analysis via analysis of intermolecular binding energy components by functional B3LYP in association with split valence basis set using polarization functions (Def2 -SVP). The whole calculations were performed with the ORCA quantum chemistry package. LIGPLOT program was utilized to monitor the intermolecular interactions.
Results: Studied AQs exhibited different binding modes/energies through hydrophilic/hydrophobic binding pockets of macromolecular targets. It was revealed that hydrophobic nature of AQ core structure facilitated interactions with residues of c-Met kinase, PKC and Akt active sites. Furthermore; appropriate substitution of hydroxyl, carboxyl and acetate functional groups within AQ scaffold might give rise to additional H-bond attraction forces with residues of PIK3 active site and this was the case for Diacerein.
Discussion and Conclusion: Structure binding relationship studies of natural AQs with different substituents demonstrated the binding affinity of each compound that was previously proved to inhibit such targets. To our best knowledge, no studies have been dedicated to the amino acid decomposition analysis of AQs as anticancer agents and results of this study may further extend the scope of natural AQs as privileged structures in cancer chemotherapy.

Keywords: Cancer, Target, Anthraquinone, Docking, Ab initio